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Enhanced tumor outgrowth after peptide vaccination. Functional deletion of tumor-specific CTL induced by peptide vaccination can lead to the inability to reject tumors.

Toes RE, Blom RJ, Offringa R, Kast WM, Melief CJ.

Department of Immunohematology and Blood Bank, University Hospital, Leiden, The Netherlands.

CTL can play an important role in the defense against tumors. Protective CTL-mediated immunity can be established in animal tumor models after vaccination with synthetic peptides representing CTL epitopes. We now report that immunization with synthetic peptides can also lead to CTL tolerance associated with the inability to reject tumors. B6 tumor cells transformed by the human adenovirus early region 1 (Ad5E1) present an Ad5E1A- and an Ad5E1B-encoded CTL epitope to the immune system. CTL clones directed against either of these epitopes are able to eradicate established Ad5E1-induced tumors, showing that these CTL epitopes are targets of CTL that can mediate tumor regression. Here, we show that protective immunity against Ad5E1-expressing tumor cells can be established by immunization with Ad5E1-transformed cells and with an adenovirus vector containing the Ad5E1 region. Protective immunity, in either case, is associated with specific CTL memory. To test whether vaccination with synthetic peptides leads to protection against Ad5E1-expressing tumor cells, we vaccinated mice s.c. with a low dose of the Ad5E1B peptide. This peptide was chosen because the CTL response against the Ad5E1B-encoded CTL epitope contributes most to the antitumor response in B6 mice after vaccination with Ad5E1-transformed cells. Ad5E1B peptide-vaccinated mice were not protected against the outgrowth of Ad5E1-expressing tumor cells, but instead were no longer able to reject a tumor
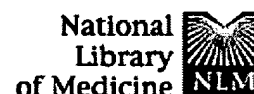
inoculum that was rejected by nonvaccinated mice. Moreover, the protection induced by tumor cell vaccination against Ad5E1B-expressing tumors was gone when the Ad5E1B-encoded CTL epitope was injected a few days before tumor challenge. This is associated with peptide-induced tolerance of Ad5E1B-specific CTL activity. These findings are relevant for the design of therapeutic approaches against both malignancies and T cell-mediated autoimmune diseases.

PMID: 8621930 [PubMed - indexed for MEDLINE]

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T-cells with specificity against neuroblastoma cells activated by
 dendritic cells.
AUTHOR: Klein-Franke A(a); Ertle F(a); Berkutzky T(a); Peters H
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JOURNAL: Blood 96 (11 Part 2):p41b November 16, 2000

ABSTRACT: Introduction: Neuroblastoma is the most frequent solid tumor in
children with a poor prognosis despite intensive, multimodal therapy. To
improve the outcome new therapeutic approaches are necessary. One new
approach in tumor therapy is the activation of cytotoxic T-cells against
tumor cells by Dendritic Cells which are by far the most effective
Antigen Presenting Cells (APC). Materials and Methods: We used the
Neuroblastoma line SK-N-LO and buffy coats of HLA-I matched blood
donors as a source for monocytes and T-cells. We isolated the monocytes
by plastic adherence and differentiated them into DC by cultivation in
the presence of GM-CSF and IL 4 (100 U/ml) and IFN gamma (50 U/ml) for 8
days. Mixed Tumor/Lymphocyte Culture (MLTC) was performed using DC as
APC that had either been pulsed with tumor cell lysate or fused to tumor
cells by PEG. T-cell proliferation was assessed by 3H-Thymidin
incorporation and the cytotoxicity of T-cells was monitored via LDH
release from tumor cells (4 hours cocultivation, effector:target ratio
10:1). Results: Without DC no activation of T-cells could be seen. In the
presence of DC pulsed with tumor cell lysate T-cells were activated
leading to a 3H-Thymidin incorporation of 3100 cpm. T-cell activation by
DC/tumor cell hybrids was even more efficient yielding 6400 cpm. In both
cases CD8+T-cells were selected and could be kept in continous culture by
restimulation with manipulated DC every 14 days, followed by culture in
the presence of IL2 for up to four cycles. Freshly activated T-cells
lysed 43% of the Neuroblastoma cells, Neuroblastoma cells with
different HLA-I formula were not lysed, nor were K562 cells. Lysis of
tumor cells was abrogated by a polyclonal rat antibody specific for
HLA-I, thus demonstrating the tumor cell lysis to be HLA-I restricted.
Discussion: We could activate cytotoxic T-cells against Neuroblastoma
cells using Dendritic Cells as APC . Hybrids of DC and tumor cells were
even more effective. Target cell lysis was antigen specific, thus the
Neuroblastoma cells can be expected to to have tumor associated
antigens. Activated T-cells killed Neuroblastoma cells in a HLA-I
depentent manner. This is particularly interesting as Neuroblastoma
cells bear only very small amounts of HLA-I molecules on their surface.
Despite of this Neuroblastoma cells are obviously a suitable target for
activated T-cells. These results could lead to clinical studies in the
therapy of Neuroblastoma using DC for the activation of tumor specific
T-cells.